permanent neonatal diabetes mellitus

Permanent neonatal diabetes mellitus is a type of diabetes that first appears within the first 6 months of life and persists throughout the lifespan. This form of diabetes is characterized by high blood sugar levels (hyperglycemia) resulting from a shortage of the hormone insulin. Insulin controls how much glucose (a type of sugar) is passed from the blood into cells for conversion to energy.

Individuals with permanent neonatal diabetes mellitus experience slow growth before birth (intrauterine growth retardation). Affected infants have hyperglycemia and an excessive loss of fluids (dehydration) and are unable to gain weight and grow at the expected rate (failure to thrive).

In some cases, people with permanent neonatal diabetes mellitus also have certain neurological problems, including developmental delay and recurrent seizures (epilepsy). This combination of developmental delay, epilepsy, and neonatal diabetes is called DEND syndrome. Intermediate DEND syndrome is a similar combination but with milder developmental delay and without epilepsy.

A small number of individuals with permanent neonatal diabetes mellitus have an underdeveloped pancreas. Because the pancreas produces digestive enzymes as well as secreting insulin and other hormones, affected individuals experience digestive problems such as fatty stools and an inability to absorb fat-soluble vitamins.

Frequency

About 1 in 400,000 infants are diagnosed with diabetes mellitus in the first few months of life. However, in about half of these babies the condition is transient and goes away on its own by age 18 months. The remainder are considered to have permanent neonatal diabetes mellitus.

Genetic Changes

Permanent neonatal diabetes mellitus may be caused by mutations in several genes.

About 30 percent of individuals with permanent neonatal diabetes mellitus have mutations in the *KCNJ11* gene. An additional 20 percent of people with permanent neonatal diabetes mellitus have mutations in the *ABCC8* gene. These genes provide instructions for making parts (subunits) of the ATP-sensitive potassium (K-ATP) channel. Each K-ATP channel consists of eight subunits, four produced from the *KCNJ11* gene and four from the *ABCC8* gene.

K-ATP channels are found across cell membranes in the insulin-secreting beta cells of the pancreas. These channels open and close in response to the amount of glucose in

the bloodstream. Closure of the channels in response to increased glucose triggers the release of insulin out of beta cells and into the bloodstream, which helps control blood sugar levels.

Mutations in the *KCNJ11* or *ABCC8* gene that cause permanent neonatal diabetes mellitus result in K-ATP channels that do not close, leading to reduced insulin secretion from beta cells and impaired blood sugar control.

Mutations in the *INS* gene, which provides instructions for making insulin, have been identified in about 20 percent of individuals with permanent neonatal diabetes mellitus. Insulin is produced in a precursor form called proinsulin, which consists of a single chain of protein building blocks (amino acids). The proinsulin chain is cut (cleaved) to form individual pieces called the A and B chains, which are joined together by connections called disulfide bonds to form insulin. Mutations in the *INS* gene are believed to disrupt the cleavage of the proinsulin chain or the binding of the A and B chains to form insulin, leading to impaired blood sugar control.

Permanent neonatal diabetes mellitus can also be caused by mutations in other genes, some of which have not been identified.

Inheritance Pattern

Permanent neonatal diabetes mellitus can have different inheritance patterns.

When this condition is caused by mutations in the *KCNJ11* or *INS* gene it is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. In about 90 percent of these cases, the condition results from new mutations in the gene and occurs in people with no history of the disorder in their family. In the remaining cases, an affected person inherits the mutation from one affected parent.

When permanent neonatal diabetes mellitus is caused by mutations in the *ABCC8* gene, it may be inherited in either an autosomal dominant or autosomal recessive pattern. In autosomal recessive inheritance, both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Less commonly the condition is caused by mutations in other genes, and in these cases it is also inherited in an autosomal recessive pattern.

Other Names for This Condition

- PNDM

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: Pancreatic agenesis, congenital
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1850096/
- Genetic Testing Registry: Permanent neonatal diabetes mellitus
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1833104/

Other Diagnosis and Management Resources

- GeneReview: Permanent Neonatal Diabetes Mellitus
  https://www.ncbi.nlm.nih.gov/books/NBK1447
- University of Chicago Kovler Diabetes Center
  http://monogenicdiabetes.uchicago.edu/

General Information from MedlinePlus

- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html
- Drug Therapy
  https://medlineplus.gov/drugtherapy.html
- Genetic Counseling
  https://medlineplus.gov/geneticcounseling.html
- Palliative Care
  https://medlineplus.gov/palliativecare.html
- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html

Additional Information & Resources

MedlinePlus

- Health Topic: Diabetes
  https://medlineplus.gov/diabetes.html

Genetic and Rare Diseases Information Center

- Permanent neonatal diabetes mellitus
  https://rarediseases.info.nih.gov/diseases/10457/permanent-neonatal-diabetes-mellitus

Additional NIH Resources

- National Institute of Diabetes and Digestive and Kidney Diseases: Monogenic Forms of Diabetes
  https://www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes/monogenic-neonatal-mellitus-mody

Educational Resources

- Disease InfoSearch: Permanent neonatal diabetes mellitus
  http://www.diseaseinfosearch.org/Permanent+neonatal+diabetes+mellitus/5681
- MalaCards: abcc8-related permanent neonatal diabetes mellitus
  http://www.malacards.org/card/abcc8_related_permanent_neonatal_diabetes_mellitus
- MalaCards: ins-related permanent neonatal diabetes mellitus
  http://www.malacards.org/card/ins_related_permanent_neonatal_diabetes_mellitus
- MalaCards: kcnj11-related permanent neonatal diabetes mellitus
  http://www.malacards.org/card/kcnj11_related_permanent_neonatal_diabetes_mellitus

Patient Support and Advocacy Resources

- American Diabetes Association
  http://www.diabetes.org/
- Diabetes UK
  https://www.diabetes.org.uk/
- International Society for Pediatric and Adolescent Diabetes
  http://www.ispad.org/

GeneReviews

- Permanent Neonatal Diabetes Mellitus
  https://www.ncbi.nlm.nih.gov/books/NBK1447

ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22permanent+neonatal+diabetes+mellitus%22

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28Diabetes+Mellitus%5BMAJR%5D%29+AND+%28permanent+neonatal+diabetes+mellitus%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D

OMIM

- DIABETES MELLITUS, PERMANENT NEONATAL
  http://omim.org/entry/606176
- PANCREATIC AGENESIS 1
  http://omim.org/entry/260370

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